

# Dr. Arrowsmith's Qualifications

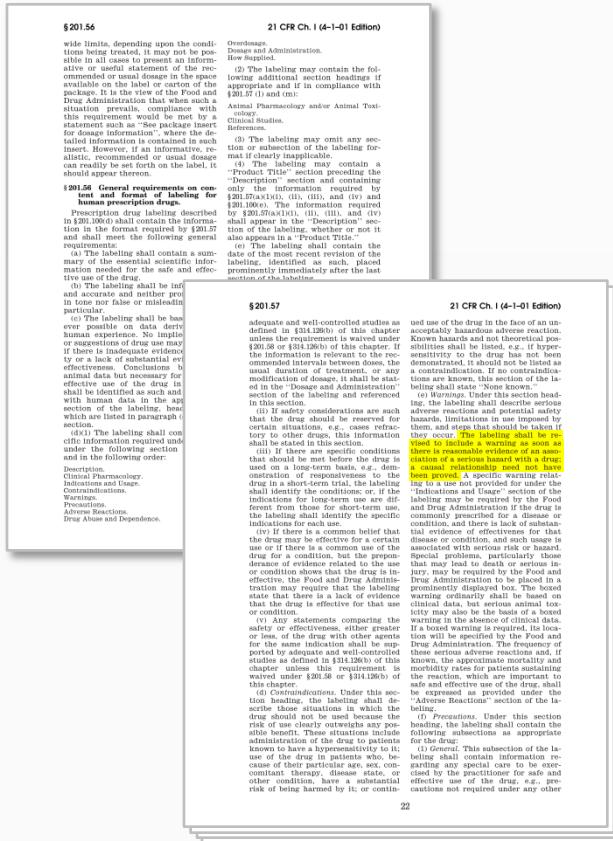
- **1984 – 1986:** Epidemic Intelligence Service Officer at the National Centers for Disease Control
- **1986 – 1988:** Staff Epidemiologist in the Office of Epidemiology and Biostatistics at the FDA
- **1988 – 1990:** Deputy Director for Office of AIDS and Special Health Concerns
- **1990 – 1991:** Senior Medical Officer for HIV at the Agency for Healthcare Policy and Research
- **1991 – 1993:** Medical Review Officer in the Division of Antiviral Drug Products in the Center for Drug Evaluation and Research
- **1995 – 1996:** Medical Review Officer in the Division of Blood Applications, Office of Blood Research and Review in the FDA Center for Biologics Evaluation and Research
- **1986 – 1996:** Faculty at Georgetown Medical Center

# Opinions of Dr. Arrowsmith

- The Neurontin labeling was adequate under the regulations and provided appropriate information for safe and effective use
- The package insert, and the Investigator's Brochure prior to approval, included information concerning suicidal behavior and adverse effects on mood reported during clinical testing
- There was no reason for Pfizer to warn of suicidal behavior in the Neurontin labeling prior to the requirement of class labeling

# 21 CFR 201.57 (2002)

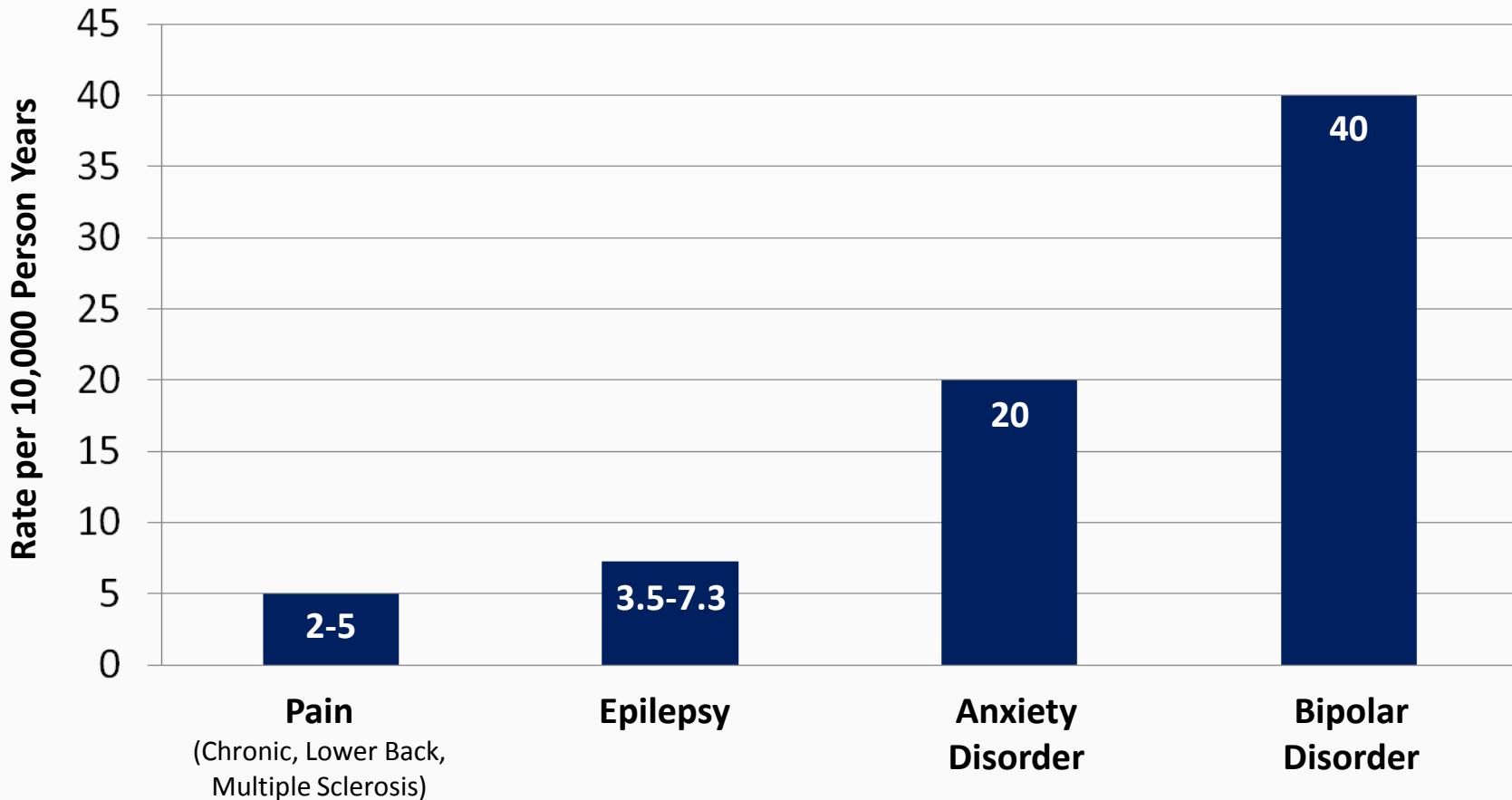
2002



The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved.

Source: 21 CFR § 201.57, Pg. 22

# Background Suicide Rates in Epilepsy, Pain, and Psychiatric Populations



Source: D.A. Fishbain, "Association of Chronic Pain on Suicide," "4 Seminars of Clinical Neuropsychiatry," 221 (1999); L. Nilsson, et al., "Risk Factors for Suicide in Epilepsy: A Case Control Study," 43 *Epilepsia* 644 (2002); A. Khan, et al., "Suicide Risk in Patients with Anxiety Disorders: A Meta-Analysis of the FDA Database," 68 *Journal of Affective Disorders* 183 (2002); L. Tondo, et al., "Suicidal Behavior in Bipolar Disorder: Risk and Prevention," 15 *CNS Drugs* 1403 (2003)

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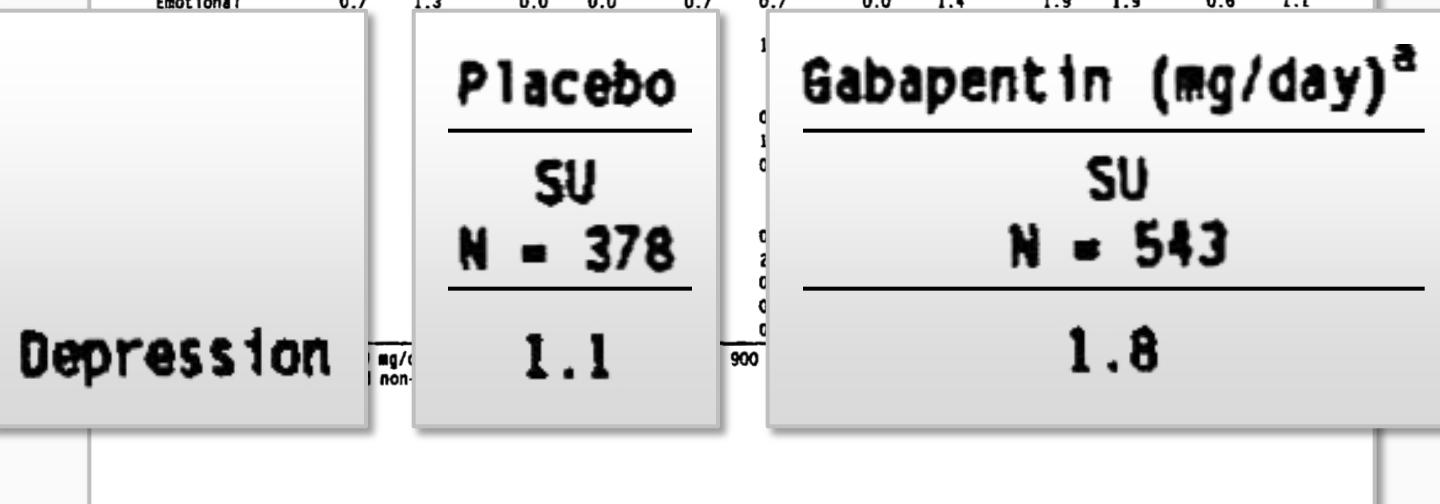
# Randomized Controlled Trials (RCTs) And Uncontrolled Trials

- A randomized controlled trial (RCT) is a study in which subjects are allocated at random (by chance alone) to receive either the medicine under study or a control medicine, typically a placebo (sugar pill)
- In a double-blind RCT, neither the subject nor the physician knows which pill the subject is getting
- An uncontrolled study is one in which there is no comparison of the treatment medicine to a placebo

# First Safety Update

TABLE 9. Summary of All Adverse Events in  $\geq 1\%$  of Gabapentin-Treated or Placebo-Treated Patients in Placebo-Controlled Add-On Therapy Studies, by Body System and Treatment Group  
(% of Patients)  
(Page 3 of 4)

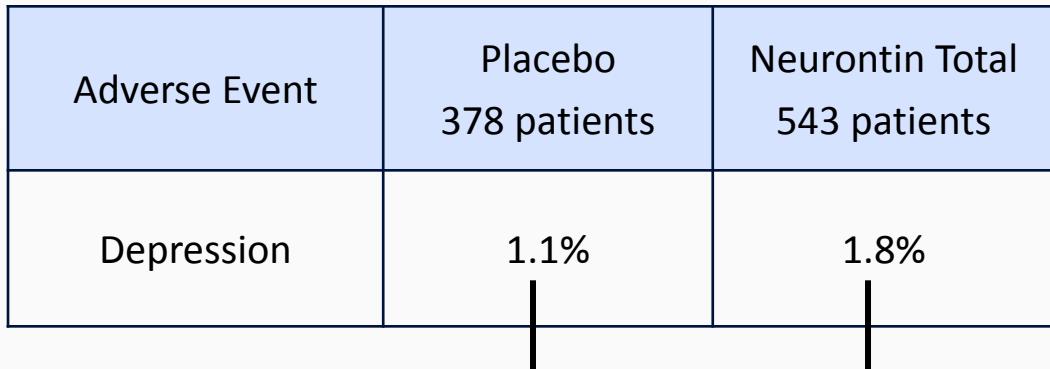
BODY SYSTEM Adverse Event	Placebo		600		900		1200		1800		Total	
	NDA	SU	NDA	SU	NDA	SU	NDA	SU	NDA	SU	NDA	SU
	N = 307	N = 378	N = 53	N = 53	N = 147	N = 147	N = 231	N = 289	N = 54	N = 54	N = 485	N = 543
<b>PSYCHOBIOLOGIC FUNCTION</b>												
Nervousness	2.0	1.9	5.7	5.7	2.0	2.0	1.3	1.7	3.7	3.7	2.3	2.4
Depression	1.0	1.1	0.0	0.0	1.4	1.4	1.3	1.7	5.6	5.6	1.6	1.8
Thinking Abnormal	1.3	1.3	1.9	1.9	1.4	1.4	2.2	1.7	1.9	1.9	1.9	1.7
Emotional	0.7	1.3	0.0	0.0	0.7	0.7	0.0	1.4	1.9	1.9	0.6	1.1



# There Is No Evidence of an Increased Risk Of Depression With Neurontin

May 29, 1992

TABLE 9. Summary of All Adverse Events in >1% of Gabapentin-Treated or Placebo-Treated Patients in Placebo-Controlled Add-On Therapy Studies by Body System and Treatment Group (N of Patients) (Page 3 of 4)											
BODY SYSTEM	Placebo	Gabapentin (mg/day)*			Placebo			Gabapentin (mg/day)*			Total
		600	900	1200	600	900	1200	600	900	1200	
Adverse Event	N=378	N=53	N=53	N=53	N=47	N=47	N=47	N=231	N=289	N=289	N=485 (n=543)
Psychiatric Function											
Depression	2.0	3.7	5.7	6.7	2.0	2.0	1.3	1.7	3.7	3.7	2.3
Thinning	1.0	1.3	1.9	1.9	1.0	0.9	1.1	1.3	1.7	1.7	1.1
Mania											
Emotion	0.7	1.3	0.9	0.9	0.7	0.7	0.6	1.4	1.9	1.9	0.6
Lability	1.6	1.3	0.0	0.0	1.4	1.4	0.4	0.7	0.0	0.0	0.6
Anxiety											
Respiratory System											
Respiritis	3.9	3.7	7.5	7.5	0.0	0.0	4.8	3.8	13.0	13.0	4.5
Pharyngitis	1.3	1.6	3.6	3.8	1.4	1.4	3.5	3.1	3.7	3.7	2.9
Coughing	1.6	1.3	3.6	3.8	0.0	0.0	2.2	1.7	5.6	5.6	2.1
GI, Liver, and Appendages											
Diarrhea	1.3	1.6	3.8	3.8	0.7	0.7	0.4	1.4	1.9	1.9	1.0
Pruritis	0.7	0.5	1.9	1.9	2.7	2.7	0.9	0.7	0.0	0.0	1.4
Abdominal	0.5	0.5	0.0	0.0	0.0	0.0	2.0	0.5	0.0	0.0	1.3
Acne	1.4	1.3	0.0	0.0	0.7	0.7	1.3	1.4	1.9	1.9	1.0
Burn	1.4	1.4	0.0	0.0	0.0	0.0	0.4	0.3	1.9	1.9	0.4
*Doses of 600 and 1200 mg/day were used only in US studies, 900 mg/day was used only in non-US studies, and 1500 mg/day was used in both US and non-US studies.											



Not Statistically Significant

Source: First Safety Update, Pg. 33, Table 9

# Rate of Psychobiologic Adverse Events Higher in Placebo

May 29, 1992 Epilepsy Trials

TABLE 8. Summary of Body System Frequency for All Adverse Events in Placebo-Controlled Add-On Therapy Studies, by Treatment Group (% of Patients)												
Body System	Placebo		500		800		1200		1800		Total (%)	
	N=	%	N=	%	N=	%	N=	%	N=	%		
Body as a Whole	20,7	20.5	10,5	10.5	10,4	10.4	12,7	12.7	10,2	10.2	29.5	29.5
Cardiovascular System	1.0	1.0	1.9	1.9	4.1	4.1	3.0	3.0	3.7	3.7	2.9	2.9
Digestive System	14.7	13.8	24.5	24.5	31.8	31.8	18.2	18.2	27.6	27.6	17.9	16.9
Genitourinary System	0.3	1.1	0.0	0.0	3.4	3.4	1.3	2.1	5.6	5.6	2.3	2.6
Hemic and Lymphatic System	2.9	3.4	3.8	3.8	7.7	7.7	3.0	3.3	7.4	7.4	3.5	3.9
Metabolic System	30.0	29.4	50.1	50.1	44.2	44.2	49.4	49.7	52.0	52.0	49.5	47.5
Psychobiologic Function	8.8	9.0	11.3	11.3	5.4	6.8	5.9	7.4	13.6	13.6	7.4	7.4
Respiratory System	1.3	1.3	17.0	17.0	1.4	1.4	11.3	11.3	22.7	22.7	10.1	9.5
Skin and Appendages	9.4	9.0	13.2	13.2	5.4	5.4	11.7	11.1	13.0	13.0	10.1	9.9
Urogenital System	4.6	4.0	3.3	3.8	4.8	4.8	3.9	3.1	7.4	7.4	4.5	4.1
Special Senses	6.2	6.1	22.6	22.6	8.8	8.8	15.2	14.2	11.1	11.1	12.6	12.3
Local and Systemic Reactions	3.3	3.2	3.8	3.8	9.5	9.5	2.5	4.2	11.1	11.1	6.2	6.3
Total (%)	56.7	55.5	56.4	56.1	59.0	58.0	71.3	72.7	60.2	60.7	71.1	71.1
† Doses of 600 and 1800 mg/day were used only in US studies; 800 mg/day was used only in non-US studies; and 1200 mg/day was used in both US and non-US studies.												

Body System	Placebo 378 patients	Neurontin Total 543 patients
Psychobiologic Function	9.0%	8.3%

Source: First Safety Update, Pg. 30, Table 8

# Medical-Statistical Review Data Cutoff Over One Year Prior to Neurontin Approval

NDA #20-235 Medical-Statistical Review

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## 8.0 Safety Findings

The purpose of this section is to assess the safety data submitted in this NDA in order to identify the risks associated with the use of Gabapentin administered in the manner suggested in the proposed labeling and to determine if any additional analysis may be needed to establish the reasonable safety of the drug system. This portion of the review will attempt to distinguish those adverse effects which may be attributed to the known pharmacokinetic actions of Gabapentin from any unexpected, local, or idiosyncratic effects. The safety review focuses on data derived from clinical trials sponsored by Parke Davis in support of this NDA. This section will contain the human safety findings, analyses and interpretations, coming from individual studies, pools of relevant studies, and the entire population exposed in the sponsor's development program.

## 8.1 Methods

In evaluating the safety of gabapentin the gabapentin-exposed population was examined for the most clinically serious adverse events and the most commonly collected and reported adverse events. The safety data relied upon for the assessment of serious adverse events were the summaries and case report forms of deaths, and dropouts due to adverse events as well as tabular summaries of adverse events determined to be serious by the investigator. In addition all case report forms that were provided in reference to these were reviewed. Finally a random check through other case report forms that were provided was made to screen for serious events that might have been missed through other methods, such as those that were not labeled as serious, but were considered serious by other criteria. The population relied upon for these was the total exposed population. Additional materials that were reviewed for this analysis included the Integrated Safety Summary (NDA Vol 1.70-1.72 filed January 31, 1992), the Safety Update #1 (NDA Vol. 5.1-5.4 filed June 1, 1992), and Safety Update #2 (NDA Vol. 24.1-24.4) with the associated case report forms and tabular summaries of laboratory and adverse event data, the individual study reports of the major studies and the available CRF's as well as the extended treatment studies and the available case report forms provided for these studies.

This safety review is current as of 6/30/1992 in the drug's development except for deaths and serious adverse events which have been updated to 9/15/1992. The dates that are pertinent to this submission are shown below.

### Data Cutoff Dates for Gabapentin Submissions

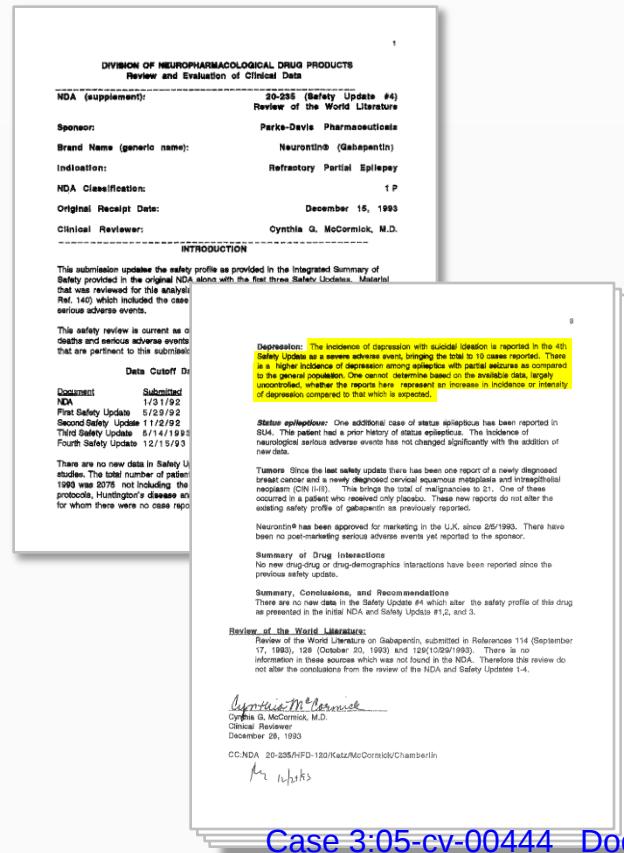
Document	Submitted	Safety Cutoff	Deaths Cutoff	Serious AF
NDA	1/3/92	4/30/90	8/31/81	6/30/91
First Safety Update	5/29/92	6/30/91	2/29/92	2/29/92
Second Safety Update	11/2/92	6/30/92	9/15/92	9/15/92

Relevant background information (noted in section 1.0) in the preclinical development of gabapentin necessitated a review of the safety data with the potential for carcinogenicity in mind. No other significant preclinical issues emerged during development, and indeed it appeared as though this drug was free of many of the adverse

This safety review is current as of 6/30/1992 in the drug's development except for deaths and serious adverse events which have been updated to 9/15/1992. The dates that are pertinent to this submission are shown below.

# Dr. McCormick's Review Of Fourth Safety Update

**December 28, 1993**



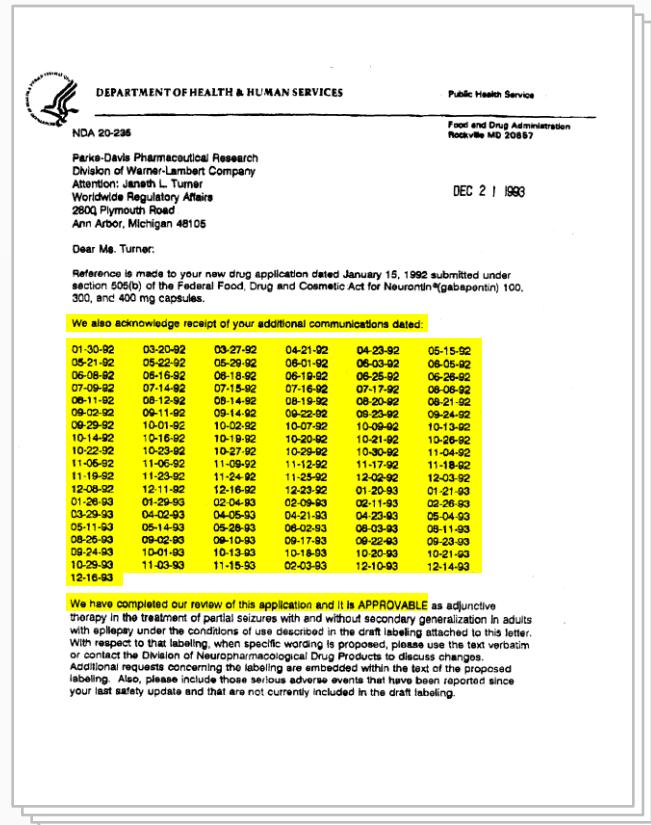
The incidence of depression with suicidal ideation is reported in the 4th Safety Update as a severe adverse event, bringing the total to 10 cases reported. **There is a higher incidence of depression among epileptics with partial seizures as compared to the general population.**

One cannot determine based on the available data, largely uncontrolled, whether the reports here represent an increase in incidence or intensity of depression compared to that which is expected.

Source: Dr. McCormick's Review of Fourth Safety Update, 12/28/93, Ex. 7562

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# The FDA Was Very Engaged During Review of the Neurontin NDA



We also acknowledge receipt of your additional communications dated:

01-30-92	03-20-92	03-27-92	04-21-92	04-23-92	05-15-92
05-21-92	05-22-92	05-29-92	06-01-92	06-03-92	06-05-92
06-08-92	06-16-92	06-18-92	06-25-92	06-26-92	
07-09-92	07-14-92	07-15-92	07-16-92	07-17-92	08-06-92
08-11-92	08-12-92	08-14-92	08-19-92	08-20-92	08-21-92
09-02-92	09-11-92	09-14-92	09-22-92	09-23-92	09-24-92
09-29-92	10-01-92	10-02-92	10-07-92	10-09-92	10-13-92
10-14-92	10-16-92	10-19-92	10-20-92	10-21-92	10-26-92
10-22-92	10-23-92	10-27-92	10-29-92	10-30-92	11-04-92
11-05-92	11-06-92	11-09-92	11-12-92	11-17-92	11-18-92
11-19-92	11-23-92	11-24-92	11-25-92	12-02-92	12-03-92
12-08-92	12-11-92	12-23-92	01-20-93	01-21-93	
01-26-93	01-29-93	02-04-93	02-09-93	02-11-93	02-26-93
03-29-93	04-02-93	04-05-93	04-21-93	04-23-93	05-04-93
05-11-93	05-14-93	05-28-93	06-02-93	06-03-93	06-11-93
08-25-93	09-02-93	09-10-93	09-17-93	09-22-93	09-23-93
09-24-93	10-01-93	10-13-93	10-18-93	10-20-93	10-21-93
10-29-93	11-03-93	11-18-93	02-03-93	12-10-93	12-14-93
12-16-93					

We have completed our review of this application and it is APPROVABLE.

# Prior to Approval, FDA Carefully Reviewed Every Word of Neurontin Label

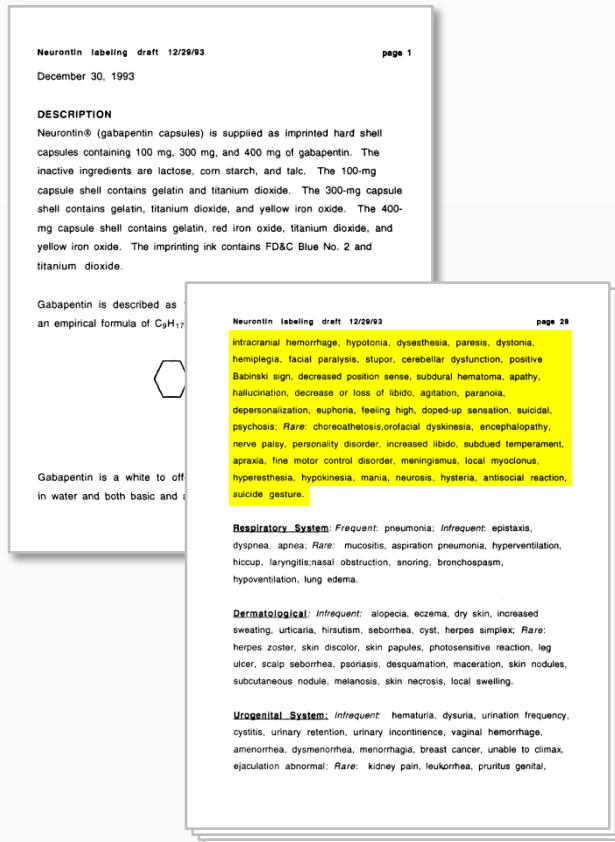
October 6, 1993

Parke-Davis		RECORD OF FDA CONTACT	
Date:	October 6, 1993	Signature	Name: Janeth L. Turner
Product Identification: (Add CI No. if known)	Gabapentin CI-945		
NDA No:	20-235	IND No:	28,454
Initiated by:	<input checked="" type="checkbox"/> P-D	<input type="checkbox"/> FDA	<input type="checkbox"/> In Person <input checked="" type="checkbox"/> Phone
FDA Contact Person:			
Name:	Nancy Chamberlain	Title:	CSO
Division:	Neuropharmacology	Phone No.:	1-301-443-3830
Purpose of Contact (Subject):			
Status of FDA review			
Summary:	<p>Dr. Katz and Dr. Leber have decided to send the approvable package to Dr. Temple prior to negotiating labeling with us. The original version of the felbamate labeling had needed extensive revision, and attempting to work with the company to revise it prior to sending it to Dr. Temple had resulted in much confusion. They felt that the most recent revisions which we had submitted on September 3 were very good and developing an FDA version based on this, sending it to Dr. Temple as part of the approvable package, and then sending it to us to begin negotiations would be the most expeditious method.</p> <p>They have not yet sent the approvable package to Dr. Temple. There is nothing which FDA needs from us prior to sending the letter. The delay appears to be fine-tuning the labeling. They are reviewing every word, and since it has been so long since the Advisory Committee Meeting, sometimes they need to go back and refresh their memory as to what occurred.</p> <p>Nancy must have Dr. Katz' permission to tell me when it is sent to Dr. Temple. Nancy will follow up with Dr. Katz to determine if she can so inform me. Unless we instruct FDA otherwise, the approvable letter will be addressed to me. Nancy will call me when it is signed and send me a FAX of the letter once it is date stamped.</p>		
 EXHIBIT Turner 15 10-11-07		WLC_JTurner_000717	

They have not yet sent the approvable package to Dr. Temple. There is nothing which FDA needs from us prior to sending the letter. The delay appears to be fine-tuning the labeling. They are reviewing every word, and since it has been so long since the Advisory Committee Meeting, sometimes they need to go back and refresh their memory as to what occurred. **They are reviewing every word**, and since it has been so long since the Advisory Committee Meeting, sometimes they need to go back and refresh their memory as to what occurred.

Source: October 6, 1993 Record of FDA Contact, WLC\_JTurner\_000717

# FDA-Approved Label Told Physicians of Reported Suicidality Events, Regardless of Cause



December 30, 1993

[I]ntracranial hemorrhage, hypotonia, dysesthesia, paresis, dystonia, hemiplegia, facial paralysis, stupor, cerebellar dysfunction, positive Babinski sign, decreased position sense, subdural hematoma, apathy, hallucination, decrease or loss of libido, agitation, paranoia, depersonalization, euphoria, feeling high, doped-up sensation, **suicidal**, psychosis; **Rare:** choreoathetosis, orofacial dyskinesia, encephalopathy, nerve palsy, personality disorder, increased libido, subdued temperament, apraxia, fine motor control disorder, meningismus, local myoclonus, hyperesthesia, hypokinesia, mania, neurosis, hysteria, antisocial reaction, **suicide gesture**.

# FDA-Approved Epilepsy Label Told Physicians About Reported Depression on Neurontin and Placebo

**Table 1. Treatment-Emergent Adverse Event Incidence in Controlled Add-On Trials (Events in at least 1% of Neurontin patients and numerically more frequent than in the placebo group)**

TABLE 1. Treatment-Emergent Adverse Event Incidence in Controlled Add-On Trials (Events in at least 1% of Neurontin patients and numerically more frequent than in the placebo group)		
Body System/ Adverse Event	(Page 1 of 2)	
	Neurontin <sup>a</sup> N = 543	Placebo <sup>a</sup> N = 378
<b>Body As A Whole</b>		
Fatigue	11.0	5.0
Headache Increase	9.8	1.6
Back Pain	1.8	0.5
Peripheral Edema	1.7	0.5
<b>Cardiovascular</b>		
Hypertension	1.1	0.3
<b>Digestive System</b>		
Dyspepsia	2.2	0.5
Diarrhea, Stool Dry	2.7	0.5
Constipation	1.5	0.4
Dental Abnormalities	1.5	0.3
Increased Appetite	1.1	0.8
<b>Hematologic and Lymphatic System</b>		
Leukopenia	1.1	0.5
<b>Musculoskeletal System</b>		
Migraine	2.0	1.9
Stiffness	1.1	0.8
<b>Nervous System</b>		
Somnolence	19.3	8.7
Sedation	1.1	1.9
Ataxia	12.5	5.6
Nystagmus	8.3	4.0
Tremor	6.8	3.2
Tiredness	2.4	1.9
Dysarthria	2.4	0.5
Amnesia	2.2	0.0
<b>Depression</b>	1.8	1.1
<sup>b</sup> Blurred Vision	1.7	1.3

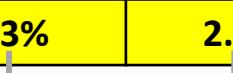
<sup>a</sup> Plus background antiepileptic drug therapy

<sup>b</sup> Amylopia was often described as blurred vision

	Neurontin N=543	Placebo N=378
Depression	1.8%	1.1%

## FDA Found a Numerically Higher Rate of Depression in Patients Given a Placebo Than Patients Treated With Neurontin in Pain Studies

## FDA Clinical Review: Treatment Emergent Adverse Events, Neuropathy and Epilepsy Add-on Studies

	All Neuropathy GPN N=820	Neuropathy Placebo N=537	Epilepsy GPN N=543	Epilepsy Placebo N=378
Depression	1.3%	2.2%	1.8%	1.1%
	 Not Statistically Significant	 Not Statistically Significant	 Not Statistically Significant	 Not Statistically Significant

Source: May 24, 2002 FDA Clinical Review, Pg. 77, Table 7.20

# FDA's 2005 'Minor' Change to Suicide-Related Adverse Event Terms in Neurontin's Labeling



November 22, 2005 E-Mail From FDA to Pfizer

-----Original Message-----  
From: Calder, Courtney [mailto:CalderC@cder.fda.gov]  
Sent: Tuesday, November 22, 2005 9:35 AM  
To: 'Patel, Manini'  
Cc: 'Everts, Mary Ann'; 'Phelan, Kevin (New York)'  
Subject: RE: : Neurontin clarification by phone request

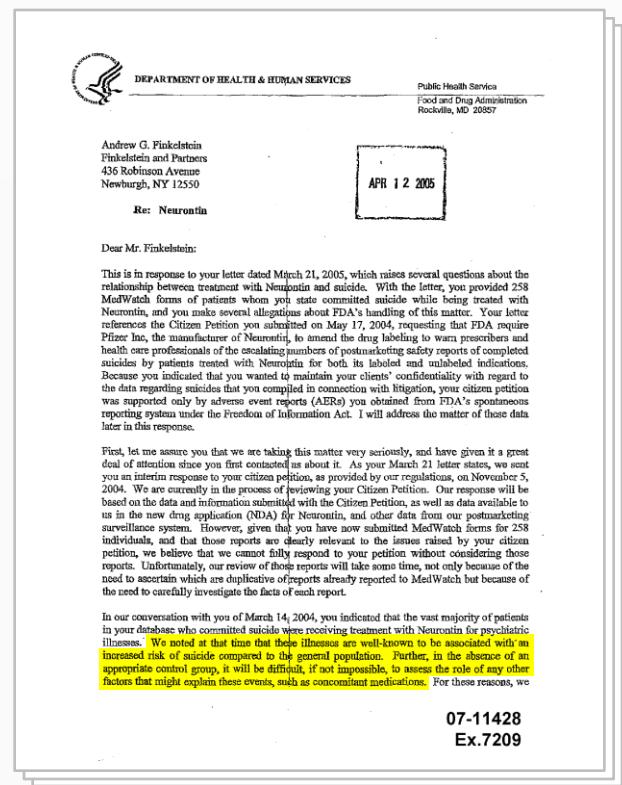
Hi Mary Ann,  
Please proceed with the minor labeling changes pertaining to suicide-related events.  
Thank you, Courtney

\*\*\*\*\*  
Courtney R. Calder, Pharm.D., LT USPHS  
Regulatory Project Manager  
Division of Neurology Products, HFD-120  
Center For Drug Evaluation and Research, FDA  
Office of Drug Evaluation I  
Ph: (301) 796-1050  
Fax: (301) 796-9842  
Email: calderC@cder.fda.gov

Please proceed with the **minor** labeling changes pertaining to suicide-related events.

Source: November 22, 2005 e-mail from Courtney Calder to Manini Patel (emphasis added)

# FDA: Controlled Trials Are Only Way to Assess Whether Neurontin Is Associated With Increased Risk of Suicide



April 12, 2005 Letter From FDA to Plaintiff's Lawyers

We noted at that time that these illnesses are well-known to be associated with an increased risk of suicide compared to the general population. **Further, in the absence of an appropriate control group, it will be difficult, if not impossible, to assess the role of any other factors that might explain these events, such as concomitant medications.**

Source: April 12, 2005 Letter from FDA to Andrew G. Finkelstein (emphasis added)

# FDA: Controlled Clinical Trials Are the Only Way to Establish Whether AEDs Are Responsible for Suicide



From: CBER DRUG INFO [mailto:CBERDRUGINFO@fda.hhs.gov]  
Sent: Tuesday, April 01, 2008 6:20 AM  
To: spcnd@comcast.net  
Subject: Antiepileptic drugs

Dear Dr. Ruggieri:

Thank you for writing to the Food and Drug Administration (FDA). This is in response to your e-mail dated February 8, 2008, to Dr. Steven Galano, regarding your scientific concerns about the recent FDA alert concerning an increased risk of suicidal behavior and suicidal ideation in patients taking antiepileptic drugs. Your e-mail was forwarded to the Division of Drug Information (DDI) for a response.

In the near future, the FDA plans to hold an advisory committee meeting to discuss the current issues involving antiepileptic drugs. The primary purpose of the meeting will be to (1) make public the detailed results of the review of the [2] information that have been submitted why, and (2) seek the committee's advice on whether any actions are appropriate and if any additional measures need to be taken. Our goal is to have the sponsors adopt the labeling changes for antiepileptic drugs by the time the meeting takes place, although we can not predict that this will be the case.

Portions of advisory committee meetings (depending on what is being discussed) are open to the public and oral presentations from the public are welcomed and encouraged. If you feel strongly about the class labeling change being implemented for antiepileptic drugs, I would suggest that you attend and/or present at the upcoming meeting.

If you are interested, please continue to visit <http://www.fda.gov/ucm/advisory/default.htm> for information on when the meeting will take place. The Peripheral and Central Nervous System Drugs Advisory Committee will be at least one of the committees involved. The "agenda" of meeting will provide the meeting location and the actions if you wish to present. In addition, transcripts and summary of minutes are usually available 30 days after the meeting and are also available from this site.

Concerning your question why data from the FDA Adverse Event Reporting System (AERS) has not been analyzed or made public, the agency does not believe that spontaneous post-marketing reports can be interpreted appropriately in this situation. Patients taking these drugs have a high background rate of suicidal thoughts/behaviors, and it is not possible to tell from AERS reports, whether the drug caused them. In the agency's view, the only way to

April 1, 2008 Letter From FDA

Concerning your question why data from the FDA Adverse Event Reporting System (AERS) has not been analyzed or made public, **the agency does not believe that spontaneous post-marketing reports can be interpreted appropriately in this situation. Patients taking these drugs have a high background rate of suicidal thoughts/behaviors, and it is not possible to tell from AERS reports, whether the drug caused them. In the agency's view, the only way to establish whether or not the drugs are responsible for suicidality is to analyze controlled trial data.**

Source: April 1, 2008 Letter from FDA to Dr. Alex Ruggieri (emphasis added)

# FDA: Use Placebo-Controlled Trials Because Post-Marketing Data Are Uninterpretable

PAGE 103

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lot of other compounds used in the United States that actually are not in this list per se. The data are obviously from more recently studied compounds and development programs.

My question is what potentially is the impact of the missing data--that is, the data from compounds in common use in the United States that are really not in this data set--and has there been an attempt to look at weaker data sets, say, the postmarketing vigilance database, to see whether or not there are some trending signals there because, obviously, we can't get at recent study data for these other compounds.

DR. KATZ: We have looked in at least one case of one drug at postmarketing for other purposes, and didn't convince ourselves that there was a signal. But I think we have long ago decided that postmarketing data are not the right data to look at, or we don't believe that for these sorts of things where there is a high background rate of suicidality so defined in these populations, I think we have concluded that postmarketing data is uninterpretable, and that is why we went to placebo-controlled trials.

It is impossible to know what the impact of other

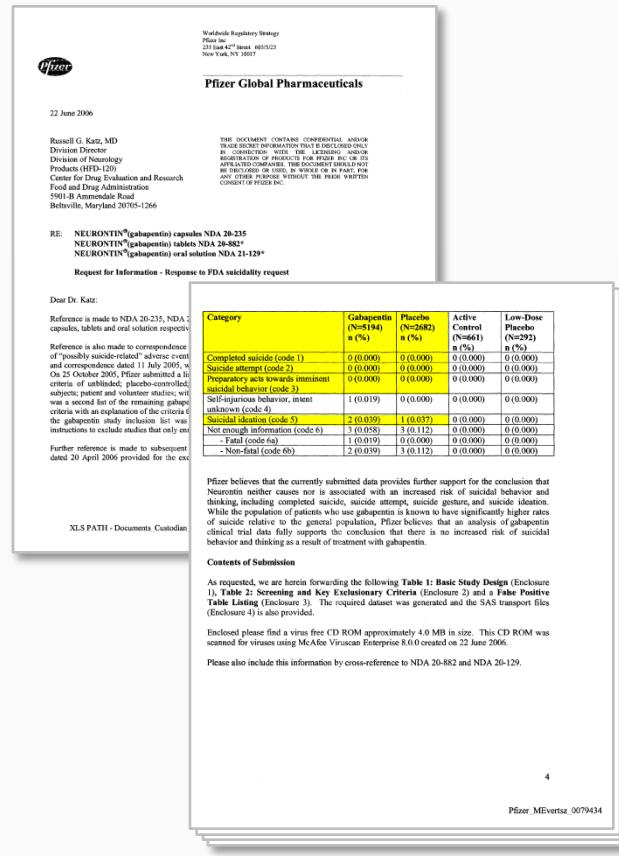
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Dr. Katz: "...we have long ago decided that **post[-]marketing data are not the right data to look at**, or we don't believe that for these sorts of things where there is a high background rate of suicidality so defined in these populations, I think we have concluded that **post[-]marketing is uninterpretable**, and that is why we went to placebo-controlled trials."

Source: July 10, 2008 FDA Advisory Committee Meeting Transcript, Pg. 103

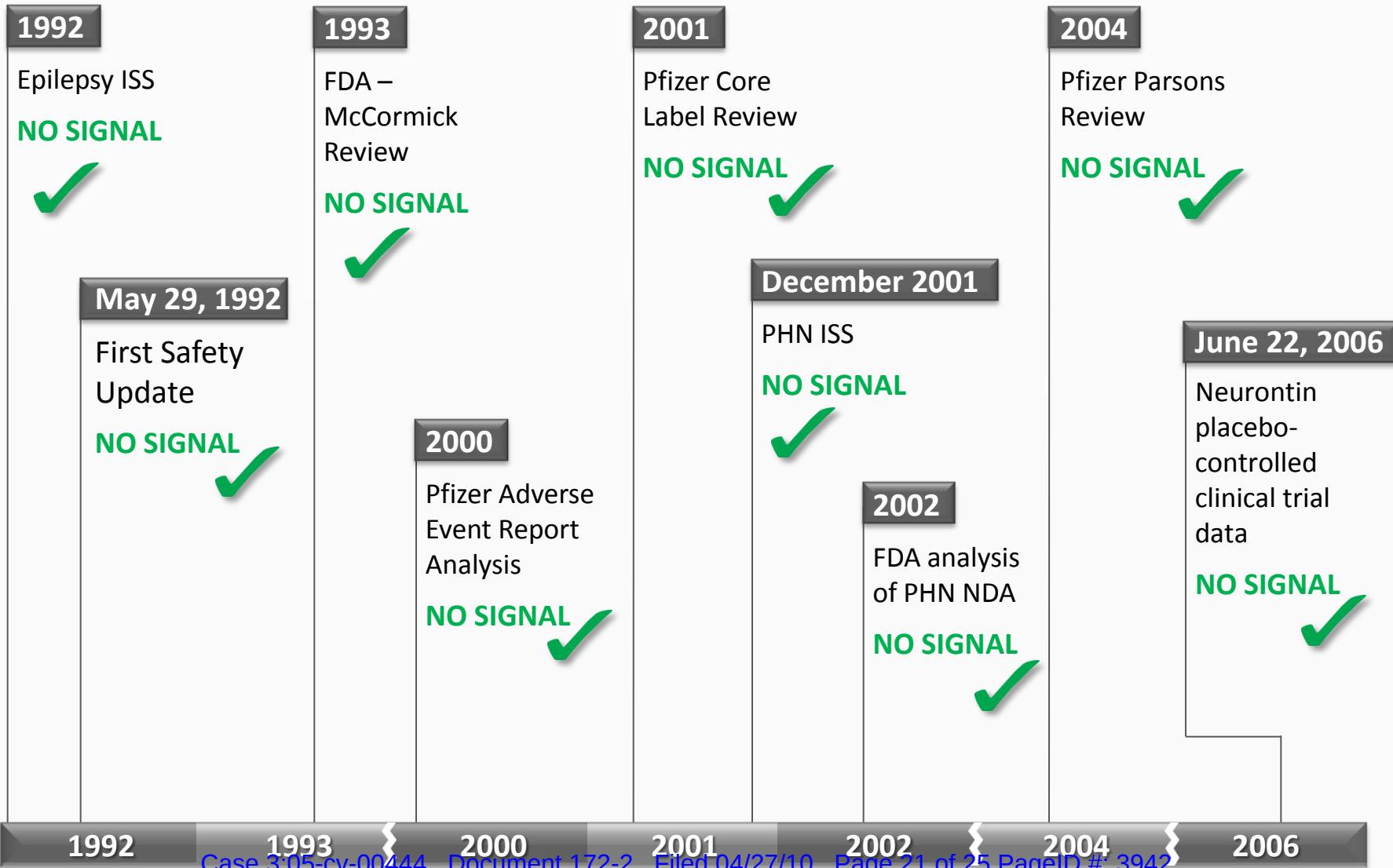
# Controlled Trials: No Increased Risk of Suicide With Neurontin

June 22, 2006



Category	Neurontin: 5,194 patients	Placebo Control: 2,682 patients
Completed suicide	0	0
Suicide attempt	0	0
Preparatory acts towards imminent suicidal behavior	0	0
Suicidal ideation	2 (0.039) [2 out of 5,194 patients]	1 (0.037) [1 out of 2,682 patients]
Total	0.039%	0.037%

# Evaluations of Depression and Suicidality



# FDA Meta-Analysis – Entire Data Necessary to Draw Conclusions

**DR. TWYMAN:** I have a question for the statisticians. Let's assume that the effect is generalizable to the class of AEDs. But, if you look at the compounds individually, could one draw the conclusion individually that compounds have a risk, or do you need the entire data set of all the AEDs put together in order to draw the conclusion that AEDs have a signal?

**DR. LEVISON:** I would say that we need the entire data set in this case.

Source: July 10, 2008 FDA Advisory Committee Meeting Transcript, Pp. 183-184

# December 16, 2008 – FDA to Physicians: FDA Has Not Concluded AEDs Cause Suicidal Behaviors



**FDA** U.S. Food and Drug Administration Department of Health and Human Services

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Information for Healthcare Professionals  
Suicidal Behavior and Ideation and Antiepileptic Drugs

**FDA ALERT [1/31/2008 Updated: 12/16/2008]:** The FDA has completed its analysis of reports of suicidality (suicidal behavior or ideation [thoughts]) from placebo-controlled clinical trials of drugs used to treat epilepsy, psychiatric disorders, and other conditions. Based on the outcome of this review, FDA is requiring, under the authorities granted under the Food and Drug Administration Amendments Act (FDAAA) of 2007, that all manufacturers of drugs in this class include a Warning in their labeling and develop a Medication Guide to be provided to patients prescribed these drugs to inform them of the risks of suicidal thoughts or actions.

The drugs affected by these safety labeling changes are commonly referred to as antiepileptic or anticonvulsant drugs (see the list below). FDA's pooled analyses of 199 clinical trials of eleven antiepileptic drugs used as mono- and adjunctive therapies showed that patients who were randomized to receive one of the antiepileptic drugs had almost twice the risk of suicidal behavior or ideation (0.43%) compared to patients randomized to receive placebo (0.24%). This increase in the risk of suicidal thoughts or behavior represents the occurrence of approximately one additional case of suicidal thinking or behavior for every 530 patients treated with an antiepileptic drug.

The risk of suicidal thoughts or behavior was generally consistent among the eleven drugs analyzed and was observed in patients who were treated for epilepsy, psychiatric disorders, and other conditions. The relative risk for suicidal thoughts or behavior was higher in the clinical trials for epilepsy compared to trials for psychiatric or other conditions. However, the absolute risk differences were similar in the clinical trials for epilepsy and psychiatric indications. The increased risk was observed as early as one week after starting antiepileptic drug treatment and throughout the observed duration of treatment.

The increased risk of suicidal thoughts or behavior was generally consistent among the eleven drugs with varying mechanisms of action and across a range of indications. This observation suggests that the risk applies to all antiepileptic drugs used for any indication.

All patients who are currently taking or starting on any antiepileptic drug for any indication should be monitored for notable changes in behavior that could indicate the emergence or worsening of suicidal thoughts or behavior or depression.

This information reflects FDA's current analysis of available data concerning these drugs. Posting this information does not mean that FDA has concluded there is a causal relationship between the drug products and the emerging safety issue. Nor does it mean that FDA is advising health care professionals to discontinue prescribing these products. FDA intends to update this document when additional information or analyses become available.

*Posting this information does not mean that FDA has concluded there is a causal relationship between the drug products and the emerging safety issue. Nor does it mean that FDA is advising health care professionals to discontinue prescribing these products. FDA intends to update this document when additional information or analyses become available.*

Source: "Information for Healthcare Professionals: Suicidal Behavior and Ideation and Antiepileptic Drugs," December 16, 2008, Ex. 7558

# Blume's 'Red Flags' Have No Credibility

Blume "Red Flag"	FDA Evaluated?	FDA Found Signal for Suicidality?
Dechallenge/ Rechallenge	YES	NO
Spontaneous Reports/PRR	YES	NO
Biologic Plausibility	YES	NO
1992 FDA Clinical Review	YES	NO
Clinical Trial Withdrawal	YES	NO
FDA Alert	YES	Yes (Class Label)

# Opinions of Dr. Arrowsmith

- The Neurontin labeling was adequate under the regulations and provided appropriate information for safe and effective use
- The package insert, and the Investigator's Brochure prior to approval, included information concerning suicidal behavior and adverse effects on mood reported during clinical testing
- There was no reason for Pfizer to warn of suicidal behavior in the Neurontin labeling prior to the requirement of class labeling